Initially, the Examiner points out that various trademarks have been used in the application and that such terminology should be capitalized. In response, Applicant notes that he has amended the specification to capitalize the trademarks set forth therein.

The Examiner next objects to the specification as purportedly not complying with §1.821(d) of the Sequence Rules and Regulations. In response, Applicant notes that the appropriate sequence identifiers have been inserted in Table 3 as well as in the description of Figures 18 and 20.

Claims 38 and 70 have been objected to as not complying with §1.821(d) of the Sequence Rules and Regulations in not setting forth the sequence listing number in the claim. In response, Applicant notes that these claims have been amended to include the sequence identifiers.

Claim 38 has been objected to as improperly depending from canceled claims. Applicant notes that such improper dependency has been amended.

Claim 36 has been objected to as reciting the trademark "SEPHACRYL S300®." Applicant refers the Examiner to MPEP §608.01(v) which indicates that names in trade are permissible in patent applications if (A) their meanings are established by an accompanying definition which is sufficiently precise and definite to be made a part of a claim, or (B) in this country, their meanings are well-known and satisfactorily defined in the literature. In the present case,

Applicant notes that the trademark SEPHACRYL S300® indeed is one which identifies a specific product and therefore is properly recited in the claim. In this regard, applicant refers the Examiner to the attached copy of a Pharmacia Biotech catalog describing SEPHACRYL gel filtration media.

Claims 36-47 and 68-70 stand rejected under 35 USC §101 as the claim is purportedly directed to a non-statutory matter. In response to the Examiner's helpful suggestion, Applicant notes that he has amended Claim 36 to recite that the protein is "isolated".

Claims 36-47, 62, and 66-70 stand rejected under 35 USC §112, second paragraph, as purportedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The specific terms and phrases subjected to that rejection will be addressed in the order in which they were raised by the Examiner.

Claim 36 has been rejected with respect to its recitation that the protein "has to comply with at least the features etc." and for its use of terms such as "at least" and "maybe." In response, Applicant notes that Claim 36, as amended, makes clear which properties are required (inducing differentiation and the recited molecular weight range) and which properties are optional (expression of the mRNA; encoding by a cDNA comprising repeat sequences and including mRNA species of different length).

Claims 36 and 39 are rejected with respect to the phrase "may be isolated from." Such terminology has been deleted.

Claim 36 has also been rejected with respect to the recitation of "characteristic repeat structures." As amended, the claim now recites that the cDNA comprises repeat sequences. Repeat sequences, of course, are well known in the art and it is submitted that a person skilled in the art could readily determine, looking at a particular cDNA, whether such cDNA included repeat sequences. It is simply a matter of looking for sequences which are repeated. Thus, the Notice requirement of 35 USC §112, second paragraph, is satisfied. The fact that a particular repeat sequence is not identified in Claim 36 is not believed to be relevant in this regard.

Claim 36 also stands rejected with respect to the recitation of "the cDNA encoding the protein." As amended, Claim 36 recites that the protein "is encoded by a cDNA comprising repeat sequences." Once again, a person skilled in the art, in possession of a cDNA, would readily appreciate whether such cDNA which encoded the protein included repeat sequences.

Claim 36 also stands rejected as being indefinite with respect to the recitation of "corresponding mRNA species of different length consisting of identical 3' regions but different 5' regions". This simply means that the variable regions are found at the 5' end of the mRNA. Once again a person skilled in the

art, looking at different length mRNA species, would readily be able to determine whether they were identical at the 3' but different at the 5' end.

Claim 37 is considered indefinite with respect to the recitation of "corresponding mRNA ." Such language has been deleted from the claim.

Claim 37 has also been rejected with respect to the recitation of "showing stable *in vitro* expression of the corresponding mRNA etc." The claim as amended now recites "that the protein is encoded by a corresponding mRNA which shows a stable *in vitro* expression if an allogeneic spleen cell reaction is carried out etc." Once again, a person skilled in the art in possession of such mRNA could readily determine if such mRNA is expressed stably in *vitro* and of conditions recited therein.

Claims 38 and 40 have been rejected with respect to the lack of a stringency standard set forth therein. It will be appreciated Claims 38 and 40 both recite that hybridization is carried out under stringent conditions.

Claims 42 and 62 stand rejected in reciting portions, analogues, and derivatives of the proteins. Applicant of course was simply claiming variants (including both analogues, derivatives and truncations) which still have the function of the protein of Claim 36. To make this clearer, Applicant has amended the claim to recite "variants of said protein comprising an amino acid sequence which is sufficiently similar to that of the protein of Claim 36 so as to exhibit

differentiation-inducing activity." It is noted that such language is commonly used in such instances as evidence by reference to attached U.S. Patent No. 5,760,181.

Claim 42 stands rejected with respect to the recitation of "fusion proteins each coding for a protein." Fusion proteins, of course, are well understood in the art as comprising two different proteins. In view of the dependency of Claim 42 on Claim 36, it is manifest that such fusion proteins will still possess the properties recited in Claim 36. Furthermore, Applicant has deleted the rejected recitation that the fusion proteins code for a protein.

Claims 42, 47, 62, 66, and 67 stand rejected with respect to the recitation "having at least differentiation-inducing activity etc." As amended, it is believed to be clear that the protein recited in these claims possesses properties in addition to those which are required in Claim 36. For example, the partial sequence may further include growth factor activities or colony-stimulating activity.

Claims 43 and 44, directed respectively to the protein having an essentially purified, native form and the protein having an essentially recombinant form, were rejected as purportedly being unclear as to what physical properties are imparted to the claimed protein in "native form" or "recombinant form." In response, applicant refers the Examiner to *Ex parte*

Aggarwal, 23 USPQ2d 1335, 1336-37 (BPAI 1992), which noted that recombinant and naturally occurring proteins indeed may possess different structure and properties, such as in the case of glycosylation. This was a logical extension of the doctrine set forth in *In re Papesch*, 137 USPQ 43 (1963) that a compound and its properties are inseparable, such that a difference in properties necessarily translates into a difference in structure. In the present case, applicant has observed that the recombinant and naturally occurring proteins indeed do possess different properties. Without being limited to theory, it is believed that the native protein is a homodimer while the recombinant *E. coli* protein is a monomer. Thus, Claims 43 and 44 properly define two different proteins having different properties, thereby complying with the requirements of 35 U.S.C. §112, second paragraph.

Applicant has also clarified Claim 45 with respect to the recitation "and/or" to make clear which properties are and are not required.

Claim 47 likewise has been amended to make clear which properties are and are not required.

Claim 62 no longer recites a therapeutic means, but rather, recites a therapeutic composition and further recites that the active component is present in an amount "effective to treat diseases accompanied by impairment of differentiation inducing activity in erythropoietic cells."

Claim 66 has been amended to make it clear as to which properties the fusion protein does and does not include.

Claim 67 no longer recites a "synthetic" protein and furthermore has been amended to make clear as to which properties it possesses.

Claim 68 has been rejected with respect to the recitation of "or inhibitors of said protein." Applicant points out that an inhibitor is simply a molecule which undermines the activity of a protein. Such terminology is routinely used in this art and a person skilled in the art would readily appreciate if a compound had such activity. In this regard, applicant makes reference to merely one example of this in U.S. Patent No. 5,872,223. Numerous other examples are available demonstrating that it is well understood in the art what is meant by an inhibitor. As set forth in *Andrew Corp. v. Gabriel Electronics*, 6 USPQ2d 2010, 2013 (Fed. Cir. 1988), if the claims, read in light of the specification reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is precise as the subject matter permits, the courts can demand no more. Once indicia of the fact that a term employed in a claim would be well understood by a person skilled in the art occurs where words similar to those used in the claims appear in prior art patents dealing with similar technology. This demonstrates that one of ordinary skill in the art would know the meaning of such terms.

Claim 68 stands rejected with respect to how the recitation of use further modifies the claim. That rejection has been rendered moot by virtue of the cancellation of Claim 68.

With respect to Claim 69, Applicant notes that the claim, as amended, recites that the protein comprises at least one of the recited properties. Quite clearly, Claim 69 further limits Claim 36 in that a protein including an additional property necessarily has a structure different than a protein which does not possess such additional property. In this regard, Applicant refers the Patent Office the oft-cited doctrine that a compound and its properties are inseparable. Thus, differences in properties translate to differences in structure and therefore the properties recited in Claim 69 do indeed impart additional structural requirements on the protein.

With respect to Claim 70, it will be appreciated that the Claim now makes reference to the Sequence ID number. Furthermore, the specific nucleotides are set forth in the sequence and therefore readily ascertained by a person skilled in the art.

In view of the above, withdrawal of the rejections to the claims under 35 USC §112, second paragraph, is respectfully requested.

Claims 36-47, 62, and 66-70 also stand rejected under 35 USC §112, first paragraph, as purportedly being non-enabled. That rejection, to the extent applied against the claims as amended, is respectfully traversed.

To a certain extent, Applicant notes that this rejection is connected with a rejection under 35 USC §112, second paragraph, discussed above. Because the physical and functional properties of the protein are now believed to be clear, the rejection is believed to have been overcome for the reasons set forth above. Furthermore, while it is indeed the case that the preferred embodiment of the invention relates to a protein inducing differentiation in erythroleukemia cell lines, assayed by hemoglobin formation, comprising an amino acid sequence encoded by SEQ ID NO: 1, 2, or 4, applicant notes that the specification in no way is so limited. However, it is not necessary for applicant to limit the invention to the specific preferred embodiment because a person skilled in the art, without undue experimentation, could readily ascertain other proteins possessing the activity and molecular weight range of Claim 1, given the comprehensive disclosure provided in the specification. Applicant further notes that the Patent Office has failed to provide any technical explanation as to why a person skilled in the art would question enablement beyond the specific EDA factor. It is of course incumbent upon the Patent Office to provide such technical explanation and not the mere statement of conclusion. *In re Marzocchi*, 169 USPQ 367 (CCPA

1971). Here, there is no reason to doubt that other proteins with differentiation-inducing activity on erythroleukemia cell lines are not enabled.

In view of the above, withdrawal of the rejection of the claims under 35 USC §112, first paragraph, is respectfully requested.

The Examiner has also rejected Claims 36-37, 39, 43-47, 62, 66, and 68-70 under 35 USC §102(b) as being anticipated by any of WO 98/04668, Eto or Tsuji. That rejection, to the extent applied against the claims as amended, is respectfully traversed.

The present invention relates to an isolated protein with differentiation-inducing activity on Friend erythroleukemia cell lines comprising the following properties:

induces differentiation in Friend erythroleukemia cell lines with hemoglobin formation;

a molecular weight in the range of about 10-60 kDa as determined by gel filtration on Sephacryl S300®;

optionally with an expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow;

optionally is encoded by a cDNA comprising repeat sequences;

optionally with corresponding mRNA species of different length comprising identical 3' regions but different 5' regions.

It is noted that the protein is useful for the treatment of diseases accompanied by impairments of the differentiation inducing activity in erythropoietic cells.

WO 89/04668 discloses a method for modulating the rate of erythropoiesis in human hematopoietic progenitor cells using two proteins known from the literature of the state of the art. These proteins are different from EDA on both the DNA and protein level. In particular, one protein is EDF/activin A and the other is inhibin which is a differentiation inhibitor. The described system is exemplified with K562 and Friend erythroleukemia cells.

Eto et al. describes a protein which exhibits a differentiating activity toward Friend leukemia cells, called Erythroid Differentiating Factor (EDF) which is a homodimer with a molecular weight of 25,000. This EDF is identical to Activin A (the sequence disclosed in Murata et al., *PNAS, U.S.A.*, **85** 2434 1998), K. Okafuji et al., ***Exp.*** *Hematol.* ***23***, 210 (1995), but does not show any homology to the protein EDA according to the present invention.

Finally, Tsuji et al. discloses EDF and in particular a production process for the protein.

It is notoriously well established under 35 USC §102 that anticipation requires that a single reference disclose each element of the claim under consideration, either explicitly or under principles of inherency. As the above

discussion is believed to make clear, none of the references cited by the Patent Office discloses the proteins as claimed according to the present invention. Furthermore, the claimed invention is non-obvious over the cited references as they do not disclose a protein exhibiting the claimed properties nor do they provide a person of ordinary skill in the art even the remotest hint that one could obtain a DNA or protein having the properties recited in the claims.

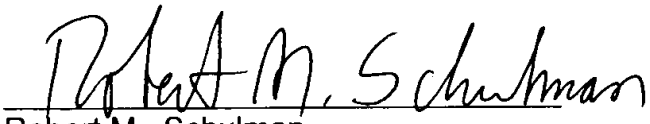
In view of the above, withdrawal of the rejection to the claims under 35 USC §102(b) is respectfully requested.

In the event that there are any questions relating to this Amendment or to the application in general, it would be appreciated if the Examiner would contact the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such Action is earnestly solicited.

The Commissioner is hereby authorized to charge fees under 37 CFR 1.16 and 1.17 (except the Issue Fee) which may be required now or hereafter, or credit any overpayment, to Deposit Account No. 19-2380.

Respectfully submitted,



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